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ARTICLE

Prevention and Treatment of Hyperuricemia with Rasburicase in Children with Leukemia and Non-Hodgkin's Lymphoma

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To prevent acute renal failure in children at risk for developing tumor lysis syndrome due to acute lymphoblastic leukemia or non-Hodgkin's lymphoma treated according to international BFM protocols, we investigated recombinant urate oxidase (rasburicase) in the first Central European open-labeled, prospective, multicenter phase IV trial. Rasburicase was administered intravenously, at 0.2 mg/kg for 5 consecutive days to 36 patients. Blood levels of uric acid, creatinine, phosphorus, calcium, lactate dehydrogenase and complete blood count were measured daily during rasburicase treatment and on days 6, 7 and 12. Initial uric acid level decreased significantly by 4 hours (from 343 µmol/L to 58 µmol/L, p<0.001), except for one steroid-resistant patient who required hemodialysis on day 14 after having introduced combined cytostatic treatment. Comparing the data of a subgroup of 12 patients receiving rasburicase with that of a historic cohort of 14 patients treated with allopurinol indicated the superiority of rasburicase over allopurinol in prophylaxis and treatment of hyperuricemia in children with leukemia and lymphoma. (Pathology Oncology Research Vol 13, No 1, 57–62)

Key words: rasburicase, uric acid, tumor lysis syndrome, leukemia, lymphoma

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Abbreviations

TLS: tumor lysis syndrome, HPOG: Hungarian Pediatric Oncology Group, BFM: Berlin-Frankfurt-Münster, ALL: acute lymphoblastic leukemia, NHL: non-Hodgkin's lymphoma, MHSCUD: Medical and Health Science Center, University of Debrecen, LDH: lactate dehydrogenase, BCP: B-cell progenitor, CBC: complete blood count, WBC: white blood cell count

Introduction

Urate oxidase has been shown to be a more effective agent than allopurinol for the prophylaxis and treatment of tumor lysis syndrome (TLS), a life-threatening complication of hyperuricemia, hyperphosphatemia and hyperkalemia occurring in pediatric patients with leukemia and lymphoma.[1] The enzyme, constitutively missing in primates, directly cleaves uric acid therefore, in vivo application of urate oxidase not only prevents uric acid formation in the course of tumor lysis, but also effectively decreases the concentration of preformed uric acid in established TLS. A further advantage of urate oxidase application, in contrast to allopurinol, is that direct cleavage of uric acid by the enzyme does not result in an ele-

vation of xantine that may cause xantine nephropathy or xantine stone formation. *Aspergillus flavus*-derived urate oxidase has indeed been proven its effectiveness for the past thirty years. However, its application has been connected with severe allergic/anaphylactic reactions in 5% of cases.[2] After early experiences, a number of well-planned and carefully executed Northern American and Western European multi-center studies demonstrated the robust uricolytic effect of the recombinant form of urate oxidase (rasburicase, Fasturtec®, Sanofi-Synthelabo, Inc., Paris, France) in children and adults with a high tumor burden.[1,3-5]

Here we report on the first Central European open-labeled, prospective, multicenter phase IV clinical trial on rasburicase prophylaxis and treatment performed in eight hematology-oncology centers of the Hungarian Pediatric Oncology Group (HPOG), a member of the International Berlin-Frankfurt-Münster (BFM) study group. Children with acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) at risk for developing TLS or suffering from TLS were investigated. The goal of the study was to investigate if a five-day-long application of recombinant urate oxidase could prevent or, in case of elevated uric acid levels on referral, effectively diminish hyperuricemia. Moreover, we intended to assess the effect of rasburicase treatment on serum creatinine, calcium and phosphorous concentrations and to investigate the development of any complication and side effect associated with the application of the drug. The results of a subgroup of patients, included in the present phase IV study, were compared to those of a historic control patient population with similar disease characteristics, receiving the standard prophylaxis and treatment of hyperuricemia consisting of allopurinol, urinary alkalinization, and hydration. As far as we know, this is the first prospective, multicenter study on the use of rasburicase in children with ALL and NHL treated according to BFM protocols.

Patients and methods

Patients

Between July 2002 and February 2003, 36 consecutive patients (boys:girls=24:12, age 4-203 months, mean 96 months) were investigated in 8 hematology-oncology centers of the HPOG, i.e. Department of Pediatrics, Medical and Health Science Center, University of Debrecen (MHSCUD), Debrecen; 1st and 2nd Departments of Pediatrics, Semmelweis University, Budapest; Department of Pediatrics, Albert Szent-Györgyi Medical and Pharmaceutical Center, Faculty of Medicine, University of Szeged, Szeged; Department of Pediatrics, University of Pécs,

Table 1. **Demographic and laboratory characteristics of study patients at presentation**

	Burkitt ALL/NHL (n=4)	*Lymphoblastic NHL (n=4)*	*Other NHL (n=2)*	*ALL (B-cell progenitor) (n=19)*	*ALL non-B-cell (n=4)*	*Total (n=33)*
Age (months)						
median	108	89	180	44	122	86
range	38-183	15-202	173-186	6-203	51-144	6-203
Sex						
male	3	3	2	12	3	23
female	1	1	–	7	1	10
Leukocyte count (G/L)						
median	10	8.1	5.9	33.2	33.6	17
range	2-33.3	5.6-9	3.5-8.2	3.5-651	5-60	2-651
LDH (U/L)						
median	1432	996	625	1071	1514	1182
range	498-4863	939-1659	384-866	415-9760	526-1975	384-9760
Uric acid (ìmol/L)						
median	370	344	263	323	172	320
range	167-1059	205-403	184-342	172-966	102-856	102-1059
Creatinine (ìmol/L)						
median	68	47	70	54	60	56
range	52-85	30-61	67-72	26-218	47-133	26-218
Calcium (mmol/L)						
median	2.4	1.9	2.3	2.4	2.1	2.4
range	2.3-2.5	1.1-2.5	2.3-2.4	2.0-4.4	2.1-2.2	1.1-4.4
Phosphorous (mmol/L)						
median	1.2	1.5	1.3	1.5	1.4	1.4
range	1-1.6	1.1-1.8	1.3-1.4	1-2.4	0.6-1.5	0.6-2.4

ALL: acute lymphoblastic leukemia, NHL: non-Hodgkin's lymphoma, LDH: lactate dehydrogenase

Pécs; Department of Pediatrics, Markusovszky Hospital of Vas County, Szombathely; Department of Hematology and Bone Marrow Transplantation, Pediatric Health Center of Borsod-Abaúj-Zemplén County Hospital, Miskolc; and Madarász Street Pediatric Hospital, Budapest. The detailed characteristics of the patients are summarized in *Table 1*. Eligibility criteria included age between 6 months and 18 years, a recent diagnosis of B-cell lineage ALL with an initial leukocyte count of at least 25 x 10^9/L, or high-grade NHL (small, non-cleaved cell, or lymphoblastic lymphomas) or any type of ALL or NHL with a plasma uric acid concentration of at least 480 mmol/L and lactate dehydrogenase (LDH) >500 IU/L, or either a serum creatinine or an LDH concentration exceeding twice the upper normal limit. Exclusion criteria were a history of clinically significant atopic allergy, bronchial asthma, glucose-6-phosphate dehydrogenase deficiency or any type of hemolytic anemia, previous treatment with rasburicase or nonrecombinant urate-oxidase, hypersensitive reactions against ingredients of the present preparation used in the study, participation in another drug experiment, pregnancy or lactation. Informed consent was obtained from parents or caretakers. The study was accepted by local ethical committees of the participating centers.

The data of a historic cohort of 14 patients with ALL and NHL having received the standard prophylaxis and treatment of hyperuricemia consisting of allopurinol, urinary alkalinization and hydration in two of the participating centers of the study, i.e. Department of Pediatrics, MHSCUD, Debrecen and 1st Department of Pediatrics, Semmelweis University, Budapest were compared with the data of those 12 study patients who were treated in the same two centers. The subset of 12 study patients, treated in the same 2 centers where the historic cohort of 14 patients were also treated, were selected for the purpose of historic comparison so as to avoid any interference that may arise from having been treated in different institutions. The 2 groups of patients were similar with respect of age, gender and white blood cell count (WBC) (*Table 2*). Mean plasma uric acid level was higher in the rasburicase group and mean serum creatinine level was higher in the allopurinol group at presentation, however, the differences were not statistically significant.

Table 2. **Characterization of 12 rasburicase- and 14 allopurinol-treated patients on admission**

Characteristics	*Rasburicase group*	*Allopurinol group*
Age (years) median	4.5	6
Male: female ratio	6:6	5:9
Lymphoma	4	1
Leukemia	8	13
WBC (G/L) median, range	51.8, 2-651	56, 0.4-551
LDH (U/L) median, range	1909, 497-9760	3193, 236-20560
Uric acid (μmol/L) median, range	323, 139-1059	207, 51-785
Creatinine (μmol/L) median, range	65, 32-85	80, 17-353
Phosphorous (mmol/L) median, range	1.32, 0.97-1.64	1.62, 0.98-3.33

Treatment design

This phase IV study was initiated and the study of the investigational new drug was approved by Sanofi-Synthelabo Inc., Budapest, Hungary.

B-cell progenitor (BCP) and T-ALL patients were treated according to either ALL-BFM 95 (before October 31, 2002) or ALL IC-BFM 2002 protocols (after November 1, 2002). Appropriate therapeutic branches of NHL-BFM 95 protocol were applied to patients with NHL or mature B-cell (Burkitt) ALL/NHL.[6,7] According to the applied protocols, non-Burkitt leukemia and lymphoma patients received a 7-day-long prednisolone monotherapy, escalating the initial 30 mg/m^2 daily dose up to 60 mg/m^2/day in 5 days, followed by the introduction of vincristine and daunorubicin on day 8 and L-asparaginase on day 12 of the protocol, in addition to the prednisolone treatment. Burkitt lymphoma/leukemia patients with a high tumor burden received a cytoreductive pre-phase treatment consisting of 5-10 mg/m^2/day dexamethasone for 5 days and 200 mg/m^2/day cyclophosphamide on 2 consecutive days followed by an intensive combined cytostatic regimen depending on the stage of the disease.

Starting on the first day of antineoplastic treatment, the patients received 0.20 mg/kg rasburicase daily to be administered in infusion during 30 minutes over 5 days. On day 1 of the study rasburicase was applied 4 hours before starting of cytoreductive therapy. On the subsequent days, rasburicase was administered directly preceding the application of antineoplastic agents.

Patients also received intravenous sodium bicarbonate (20-40 mmol/L) to maintain urine P_H between 6.5 and 7.0, and hydration (3000 ml/m^2 body surface area). The duration of the study was 12 days for each patient, including 5 days of rasburicase treatment and a final safety assessment on day 12. Control patients were given oral allopurinol instead of rasburicase in a daily dose of 300 mg/m^2 body surface area.

Follow-up protocol

Physical examination, complete blood count (CBC) including WBC (reference range: 3.5-10.5 G/L) and differential count, measurement of plasma uric acid (reference range: 200-400 μmol/L), serum creatinine (adult reference range: 62-106 μmol/L, age-dependent), calcium (reference range:

2.1-2.6 mmol/L), phosphorus (reference range: 0.8-1.45 mmol/L) and LDH levels [reference range: 230-460 U/L] as well as toxicity assessment were performed every day during rasburicase treatment and on days 6, 7 and 12 of the chemotherapy. Plasma uric acid was also measured 4 hours after the first rasburicase infusion. Abdominal ultrasound was performed on day 1 and, in case of pathological findings, on day 12. Laboratory parameters were determined at accredited clinical laboratories of the participating centers according to standard methods. Special handling procedures and strict temperature conditions (0-4°C) were observed during blood collection procedures to block ex vivo enzymatic activity of rasburicase.

Statistical analysis

Descriptive summary statistics (n, maximum, minimum, mean, median, SD and SE values) was computed. Analysis of variance was used to compare changes of different laboratory parameters during the study. P values below 0.05 were reported as statistically significant. Descriptive statistics and statistical analyses were calculated using SPSS 11 software and Statistics for Windows program.

Results

Efficacy of rasburicase

Of the 36 patients 20 had BCP ALL, 6 T-ALL, 4 lymphoblastic NHL, 4 Burkitt ALL/NHL and 2 non-lymphoblastic, non-Burkitt NHL. Each case was characterized by a massive tumor burden, as indicated by high serum LDH level or hyperleukocytosis (*Table 1*). Three of the 36 patients were dropped out of the study: a 4-month-old girl (B-cell progenitor ALL) because of her age and 2 patients (both with corticosteroid-resistant T-ALL) because of protocol violation, having administered rasburicase for 8 instead of 5 days, as scheduled in the study. The pediatric hematologist-in-charge for the latter 2 patients decided upon an extension of the rasburicase treatment for 3 additional days to avoid late-onset TLS, with the permission of the company. Thirty-three study patients completed the study. WBC (range 1.3-698 G/L, median 10 G/L, mean±SD 54±136 G/L) and serum LDH (range 312-9824 U/L, median 945 U/L, mean±SD 2087±2407 U/L) levels decreased significantly ($p<0.001$ and $p=0.01$, respectively) by the third day of the study.

Hyperuricemia at diagnosis was present in 12/33 patients (36%). Rasburicase effectively corrected or prevented hyperuricemia. The plasma uric acid concentration, assessed immediately before the application of rasburicase (range 119-856 μmol/L, median 287 μmol/L, mean±SD 342±192 μmol/L) decreased significantly (range 0-327 μmol/L, median 12 μmol/L, mean±SD 58±89 μmol/L) by 4 hours after the first rasburicase treatment ($p<0.001$). Uric acid concentrations remained low during the entire course of rasburicase treatment and within the normal range during the 7-day-long follow-up period, i.e. during the entire course of the study (*Fig. 1a*) except for one patient with steroid-resistant T-ALL who experienced a late-onset TLS starting after the introduction of additional cytostatic drugs.

This patient was presented with 856 μmol/L uric acid and 1975 U/L LDH concentration, and 18.3 G/L WBC. According to the study design, the patient was given rasburicase for 5 days in parallel with prednisolone monotherapy, as indicated by the ALL BFM-IC 2002 study protocol. WBC increased despite prednisolone treatment. Both plasma uric acid and serum creatinine levels decreased after the first rasburicase treatment and remained within the normal range until day 8, when vincristine (1.5 mg/m^2 body surface area) and daunorubicin (30 mg/m^2 body surface area) were introduced according to the antileukemic treatment schedule. Severe TLS developed outside of the time frame (i.e. 12 days) of the study and the patient required hemodialysis because of acute renal failure on day 14.

Renal impairment, defined as an abnormally high serum creatinine level (133 and 218 μmol/L, respectively), was present in 2/33 (6%) patients on referral. The high initial serum creatinine concentrations of these two patients were normalized by day 3 and 12, respectively. All other patients were admitted with a normal initial serum creatinine concentration that did not exceed the age-specific upper normal level during the entire study period.

Initial serum phosphorous levels were mildly higher than the normal range (*Table 1*) and did not change significantly throughout the 12-days study period (data not shown). Similarly, serum calcium concentrations did not change significantly during the study period although initially high serum calcium concentrations (*Table 1*) fell into the normal range after rasburicase treatment (data not shown).

Adverse events and mortality

Adverse events observed in the study patients, including grade I fever (2 patients), grade II nausea (1 patient), grade I abdominal pain (1 patient) and grade II mucositis (2 patients) were attributed to their disease and the applied chemotherapeutic regimens. One patient developed uremia due to TLS outside of the 12-day study period. Treatment with rasburicase was well tolerated. No patients experienced anaphylactic events or even mild atopic reactions. None of the patients died during the study period and the therapy was not discontinued in any of the patients.

Comparison between rasburicase and allopurinol

We performed a comparison between a subset of 12 study patients and 14 historic controls receiving allopurinol, treated in 2 of the centers participating in the study.

Patients having received rasburicase had a lower exposure to uric acid on average during the first 168 hours of therapy (*Fig. 1b*). In rasburicase-treated patients, plasma uric acid level decreased significantly (p=0.02) 4 hours after the first dose, as compared to the pretreatment uric acid concentration and it remained within the normal range throughout the study period. In allopurinol-treated patients, posttreatment plasma uric acid levels were first checked 24 hours after the application of allopurinol. At this time uric acid level concentration was not significantly different from the pretreatment value. The first significant decrease in the uric acid level in the allopurinol group was observed at 61 hours after treatment (*Fig. 1b*). In the allopurinol group, 3 patients experienced an elevation of serum creatinine levels on chemotherapy (maximum levels 131-344 μmol/L), one of them requiring hemodialysis during induction chemotherapy because of severe oliguria, hyperkalemia, hyperuricemia and hyperphosphatemia. None of the 12 patients of the rasburicase group had elevated creatinine levels after having introduced recombinant urate oxidase.

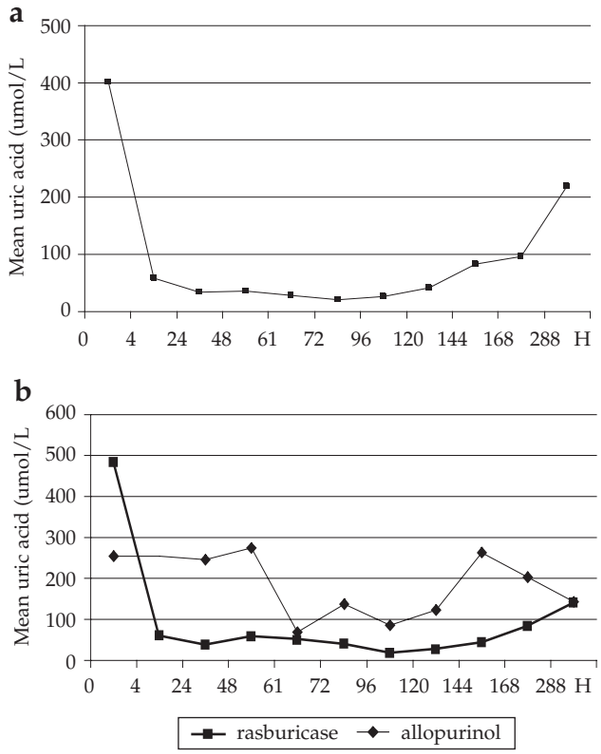

Figure 1. (a) *Uric acid control of rasburicase study patients (n=33).* ***(b)*** *Comparison of uric acid levels in patients receiving rasburicase (n=12) or allopurinol (n=14) for TLS prophylaxis and treatment*

Discussion

Recombinant urate oxidase represents a recently introduced therapeutic modality for the prophylaxis and treatment of hyperuricemia associated with hematological malignancies. Although non-recombinant urate oxidase (Uricozyme®, Sanofi-Synthelabo Inc., Paris, France) has been used for almost 3 decades, it has not become a standard practice in Hungary.[8] According to American, French and Italian studies, the dialysis rate in Burkitt lymphoma patients decreased by an order of magnitude due to the use of Uricozyme.[2,8] However, about 5% of the children given aspergillus-derived urate oxidase developed allergic reactions.[2] The introduction of the recombinant form of urate oxidase seems to have decreased allergic side effects.

Recombinant urate oxidase has been approved for pediatric use in Europe in 2001 and in Northern America in 2002. Western European and Northern American clinical trials reported on the use of rasburicase in pediatric oncology patients at risk for developing TLS.[1,3-5] Each study observed a dramatic decrease in uric acid levels following rasburicase treatment both in the prophylactic and hyperuricemic groups. In these studies rasburicase was applied as single or double daily infusion at 0.2 mg/kg for 1 to 7 consecutive days. The patients were at high risk for developing TLS i.e. initial WBC of leukemic patients was between 25-50 G/L and NHL patients had an advanced disease with a high tumor burden.[3,4] The incidence of hemodialysis decreased to virtually zero. Side effects were negligible, only few patients experienced severe adverse effects attributed to the use of the recombinant urate oxidase preparation. Recent preliminary studies suggest that rasburicase may be effective either at a smaller dose or applied for a shorter period of time than it was used in the first larger clinical studies.[3,4]

Here we report the first Central European open-labeled, multicenter phase IV study investigating the efficacy and safety of rasburicase in pediatric patients at risk for developing TLS because of lymphoid malignancies treated according to international BFM protocols. We also compared the effect of rasburicase with the conventional anti-TLS treatment/prophylaxis using a historical control population. Similarly to the Northern American and Western European trials, our phase IV clinical study demonstrated that rasburicase was a highly effective and safe uricolytic agent in a 0.20 mg/kg daily dose during 5 consecutive days in patients either presenting with hyperuricemia or having lymphoid malignancies with large tumor cell burdens, rendering them at high risk for developing TLS. Initial plasma uric acid levels of patients decreased significantly as soon as 4 hours after receiving the first dose of rasburicase and remained low during the entire 12 days of the study despite parallel administration of cytoreductive chemotherapy. Importantly, the rapid uricolytic effect of urate oxidase prevented any delay in chemotherapy due to hyper-

uricemia, a major concern in the treatment of patients with Burkitt ALL or advanced NHL.[3,4] One single patient developed a severe TLS requiring hemodialysis on day 14. This T-ALL patient proved prednisolone-resistant and his leukemic burden did not decrease until introducing additional cytostatic drugs on day 8 of treatment. None of the patients developed severe or even mild allergic reactions on rasburicase therapy.

Hyperphosphatemia with consequent hyperphosphaturia is another important cause of acute renal failure due to tumor cell lysis.[9] Similarly to the study of Pui et al.,[3] our patients experienced only mildly elevated serum phosphorous levels during rasburicase treatment and the follow-up period. We attribute this result at least in part to the use of rasburicase, since decreased precipitation of uric acid or its precursor compound, xantine in renal tubules might have improved the excretion of phosphorous.[3]

The historic comparison between rasburicase and allopurinol indicated that rasburicase was a more potent and more rapid uricolytic agent than allopurinol. Rasburicase induced a significant decrease in uric acid concentration much earlier (4 hrs) than allopurinol (61 hrs). Serum creatinine levels of patients in the rasburicase group normalized and remained low while receiving rasburicase whereas 3 of the 14 historic control patients experienced an elevation in serum creatinine levels during the application of allopurinol. One of these 3 patients developed an overt TLS requiring hemodialysis treatment.

In conclusion, this study demonstrated that rasburicase is an effective, fast acting and safe uricolytic agent for children at risk for developing TLS due to ALL and NHL treated according to international BFM protocols. The 5-day-long rasburicase therapy, as applied in this study according to the recommendation of the manufacturer, was shown to provide an effective control of hyperuricemia. Recently, small-sized studies suggested that even shorter rasburicase treatment may provide an effective control of hyperuricemia in the majority of children with leukemia and lymphoma.[10] However, a small subgroup of patients resistant to the initial anti-cancer regimen might benefit from an extended application of rasburicase until tumor control can be achieved by the application of effective cytostatic agents. In those selected cases, the extended use of rasburicase may be justified both from a professional and a financial point of view.[3,11]

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References

1. *Goldman SC, Holcenberg JS, Finkleinstein JZ, et al:* A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 97: 2998-3003, 2001
2. *Pui CH, Relling MV, Lascombes F, et al:* Urate oxidase in prevention and treatment of hyperuricemia associated with lymphoid malignancies. Leukemia 11: 1813-1816, 1997
3. *Pui CH, Mahmoud HH, Wiley JM, et al:* Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol 19: 697-704, 2001
4. *Bosly A, Sonet A, Pinkerton CR, et al:* Rasburicase (recombinant urate oxidase) for the management hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer 98: 1048-1054, 2003
5. *Pession A, Barbieri E:* Treatment and prevention of tumor lysis syndrome in children. Experience of Associazione Italiana Ematologia Oncologia Pediatrica. Contrib Nephrol 147:80-92, 2005
6. *Schrappe M, Reiter A, Zimmermann M, et al:* Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995, Berlin-Frankfurt-Munster. Leukemia 14: 2205-2222, 2000
7. *Reiter A, Schrappe M, Parwaresch R, et al:* Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage – a report of the Berlin-Frankfurt-Munster Group. Clin Oncol 113: 359-372, 1995
8. *Masera G, Jankovic M, Zurlo MG, et al:* Urate-oxidase prophylaxis of uric acid-induced renal damage in childhood leukemia. J Pediatr 7: 202-204, 1985
9. *Cohen LF, Balow JE, Magrath IT, et al:* Acute tumor lysis syndrome: A review of 37 patients with Burkitt lymphoma. Am J Med 68: 486-491, 1980
10. *Liu CY, Sims-McCallum RP, Schiffer CA:* A single dose of rasburicase is sufficient for the treatment of hyperuricemia in patients receiving chemotherapy. Leuk Res 29: 463-465, 2005
11. *Annemans L, Moeremans K, Lamotte M, et al:* Pan-European multicentre economic evaluation of recombinant urate oxidase (Rasburicase) in prevention and treatment of hyperuricemia and tumor lysis syndrome in haematological cancer patients. Support Care Cancer 11: 249-257, 2003